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(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).					
(72) Inventors; and (75) Inventors/Applicants (for US only): GASTER, Laramie, Mary [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). WYMAN, Paul, Adrian [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).					
(74) Agent: WATERS, David, Martin; SmithKline Beecham plc, Corporate Intellectual Property, 2 New Horizons Court, Brentford, Middlesex TW8 9EP (GB).					
(54) Title: ARYLPiperazine AND ARYLPiperidine DERIVATIVES, THEIR PREPARATION AND THEIR USE AS COMBINED 5-HT1A, 5-HT1B AND 5-HT1D RECEPTOR ANTAGONISTS					
(57) Abstract					
<p>The invention relates to compounds of formula (1) or a salt thereof in which R<sup>a</sup> represents the group (1) in which the ring A is 5, 6 or 7-membered carbocyclic ring optionally substituted by one or more C<sub>1</sub>-alkyl groups, fused at the 2,3 or 3,4-positions of the adjacent phenyl ring, the ring A being optionally fused to a further phenyl ring optionally substituted by one or more substituents independently selected from C<sub>1</sub>-alkyl and halo; R<sup>2</sup> is halogen, C<sub>1</sub>-alkyl, C<sub>3</sub>-cycloalkyl, C<sub>3</sub>-cycloalkenyl, C<sub>1</sub>-alkoxy, C<sub>1</sub>-alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO<sub>2</sub>R<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup> where R<sup>10</sup> and R<sup>11</sup> are independently hydrogen or C<sub>1</sub>-alkyl; a is 0, 1 or 2; L is a group of formula -Y-C(=O)-DG- or -C(=O)-DG- or -DG-C(=O)- in which Y is -NH-, NR<sup>5</sup> where R<sup>5</sup> is C<sub>1</sub>-alkyl, or Y is -CH<sub>2</sub>- or -O-; D is nitrogen, carbon or a CH group, G is hydrogen or C<sub>1</sub>-alkyl providing that D is nitrogen or a CH group, or G together with R<sup>b1</sup> forms a group W where W is (CR<sup>16</sup>R<sup>17</sup>)<sub>u</sub> where t is 2, 3 or 4 and R<sup>16</sup> and R<sup>17</sup> are independently hydrogen or C<sub>1</sub>-alkyl or W is (CR<sup>16</sup>R<sup>17</sup>)<sub>u</sub>-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, CR<sup>16</sup>=CR<sup>17</sup>, =CR<sup>16</sup>=N, CR<sup>16</sup>O, =CR<sup>16</sup>S or =CR<sup>16</sup>-NR<sup>17</sup> provided that u is not 0 when J is oxygen or sulphur; X is nitrogen or carbon; R<sup>b1</sup> and R<sup>b2</sup> are independently hydrogen, halogen, hydroxy, C<sub>1</sub>-alkyl, C<sub>2</sub>-alkenyl, C<sub>3</sub>-cycloalkyl, trifluoromethyl, C<sub>1</sub>-alkoxy or aryl, or R<sup>b1</sup> together with G forms a group W as defined above; R<sup>c</sup> is hydrogen or C<sub>1</sub>-alkyl; and ..... is a single bond when X is nitrogen or a single or double bond when X is carbon, having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.</p>					

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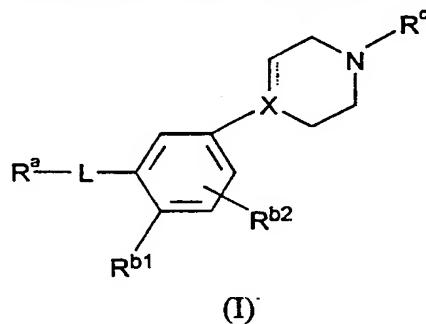
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## ARYLPIPERAZINE AND ARYLPYPERIDINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS COMBINED 5-HT1A, 5-HT1B AND 5-HT1D RECEPTOR ANTAGONISTS

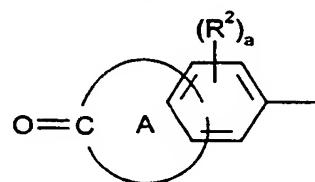
The present invention relates to novel piperazine derivatives, processes for their preparation, and pharmaceutical compositions containing them.

5 WO 95/04729, WO 95/06044 and WO 95/06637 all disclose a series of piperazine derivatives which are said to possess 5HT<sub>1D</sub> receptor antagonist activity. These compounds are alleged to be of use in the treatment of various CNS disorders such as depression. EPA 10 0533266/7/8 disclose a series of benzanilide derivatives which are said to possess 5-HT<sub>1D</sub> receptor antagonist activity. The 5-HT<sub>1D</sub> receptor was subsequently found to consist of a pair of gene products originally designated 5-HT<sub>1D $\alpha$</sub>  and 5-HT<sub>1D $\beta$</sub>  receptors which have more recently been reclassified as 5-HT<sub>1D</sub> and 5-HT<sub>1B</sub> receptors respectively (Hartig, P.R. et al., Trends in Pharmacological Sciences 1992, Vol. 13, page 152, Hartig, P.R. et al., Trends in Pharmacological Sciences, 1996, Vol. 17, page 103).

15 A structurally distinct class of compounds have now been found that exhibit combined 5HT<sub>1A</sub>, 5HT<sub>1B</sub> and 5HT<sub>1D</sub> receptor affinity. It is expected that such compounds will be useful for the treatment and prophylaxis of various disorders. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



20 in which R<sup>a</sup> represents the group:



25 in which the ring A is 5, 6 or 7 -membered carbocyclic ring optionally substituted by one or more C<sub>1</sub>-alkyl groups, fused at the 2,3- or 3,4-positions of the adjacent phenyl ring, the ring

A being optionally fused to a further phenyl ring optionally substituted by one or more substituents independently selected from C<sub>1</sub>-6alkyl and halo;

R<sup>2</sup> is halogen, C<sub>1</sub>-6alkyl, C<sub>3</sub>-6cycloalkyl, C<sub>3</sub>-6cycloalkenyl, C<sub>1</sub>-6alkoxy, C<sub>1</sub>-6alkanoyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO<sub>2</sub>R<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup>

5 where R<sup>10</sup> and R<sup>11</sup> are independently hydrogen or C<sub>1</sub>-6alkyl;

a is 0, 1, or 2;

L is a group of formula

- Y-C(=O)-DG - or -C(=O)-DG- or -DG-C(=O)-

10 in which Y is - NH -, NR<sup>5</sup> where R<sup>5</sup> is C<sub>1</sub>-6alkyl, or Y is - CH<sub>2</sub> - or - O -;

D is nitrogen, carbon or a CH group, G is hydrogen or C<sub>1</sub>-6alkyl providing that D is nitrogen or a CH group, or G together with R<sup>b1</sup> forms a group W where W is (CR<sup>16</sup>R<sup>17</sup>)<sub>t</sub> where t is 2, 3 or 4 and R<sup>16</sup> and R<sup>17</sup> are independently hydrogen or C<sub>1</sub>-6alkyl or W is (CR<sup>16</sup>R<sup>17</sup>)<sub>u</sub>-J where u is 0, 1, 2 or 3 and J is oxygen, sulphur, CR<sup>16</sup>=CR<sup>17</sup>, CR<sup>16</sup>=N, =CR<sup>16</sup>O, =CR<sup>16</sup>S

15 or =CR<sup>16</sup>-NR<sup>17</sup> provided that u is not 0 when J is oxygen or sulphur;

X is nitrogen or carbon;

R<sup>b1</sup> and R<sup>b2</sup> are independently hydrogen, halogen, hydroxy, C<sub>1</sub>-6alkyl,

C<sub>2</sub>-6alkenyl, C<sub>3</sub>-6cycloalkyl, trifluoromethyl, C<sub>1</sub>-6alkoxy or aryl, or R<sup>b1</sup> together with G forms a group W as defined above;

20 R<sup>c</sup> is hydrogen or C<sub>1</sub>-6alkyl; and

\_\_\_\_\_ is a single bond when X is nitrogen or a single or double bond when X is carbon.

C<sub>1</sub>-6alkyl groups whether alone or as part of another group may be straight chain or branched. The term 'acyloxy' is used herein to describe a group -OC(O)C<sub>1</sub>-6alkyl. The term

25 'aryl' is used herein to describe, unless otherwise stated, a group such as phenyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

In addition to the keto group and the portion fused to the phenyl ring the ring A is preferably formed from a straight chain alkylene grouping containing 2, 3 or 4 carbon atoms.

30 The ring A is preferably a 5 or 6-membered ring in which the oxo group is advantageously attached to a carbon atom adjacent to the phenyl ring, the ring A being preferably attached to the 3,4-positions of the latter phenyl ring.

a is preferably 0 or 1;

R<sup>2</sup> is preferably halogen for example a chloro group or a C<sub>1</sub>-6alkyl group for

35 example a methyl group;

The group L is preferably a group of formula:-

-Y-C(=O)-(DG)-,

in which Y is preferably -NH;

D is preferably nitrogen and G is preferably a hydrogen atom or together with R<sup>b1</sup> 5 forms a group W, preferably -(CH<sub>2</sub>)<sub>2</sub>-.

R<sup>b1</sup> and R<sup>b2</sup> are preferably hydrogen or a halogen atom for example bromine or chlorine, or a C<sub>1-6</sub>alkoxy group for example methoxy, or R<sup>b1</sup> together with G forms the group W referred to above. Preferably R<sup>b2</sup> has a para relationship with respect to the group L.

10 X is preferably nitrogen.

R<sup>c</sup> is preferably a C<sub>1-6</sub>alkyl group for example methyl.

Particularly preferred compounds according to the invention include:-

5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline,

15 5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline,

5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline,

5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline,

20 5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline,  
5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline,  
5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline,

25 5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline,

5-Chloro-1-(9-oxo-9H-fluoren-2-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline,

5-Chloro-1-(9-oxo-9H-fluoren-3-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline,

5-Methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline,

30 5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline,

5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline,

35 5-Methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline

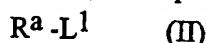
or pharmaceutically acceptable salts thereof.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

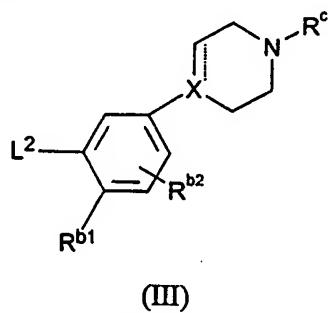
Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates.

Compounds of the invention can be prepared using procedures known in the art. In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises:

(a) where L is  $-C(=O)-DG$  - or  $-DG-C(=O)-$ , coupling a compound of formula (II):



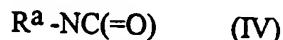
with a compound of formula (III):



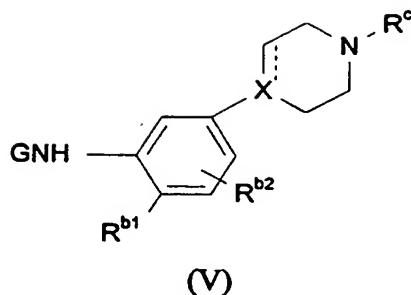
in which  $R^a$ ,  $R^b1$ ,  $R^b2$ ,  $R^c$  and X are as defined in formula (I) and  $L^1$  and  $L^2$  contain the appropriate functional groups which are capable of reacting together to form the L moiety; or

20

(b) where L is  $-Y-C(=O)-DG$  in which D is nitrogen and Y is NH, coupling a compound of formula (IV):



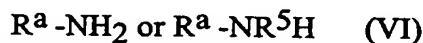
in which  $R^a$  is defined in formula (I) or a protected derivative thereof, with a compound of formula (V):



in which  $R^{b1}$ ,  $R^{b2}$ ,  $R^c$ , G and X are as defined in formula (I), or a protected derivative thereof; or

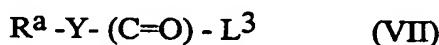
5

(c) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is NH or NR<sup>5</sup>, reacting a compound of formula (VI)



in which  $R^a$  and  $R^5$  are as defined in formula (I) with a compound of formula (V) together with an appropriate urea forming agent; or

(d) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is CH<sub>2</sub> or O, reacting a compound of formula (VII):

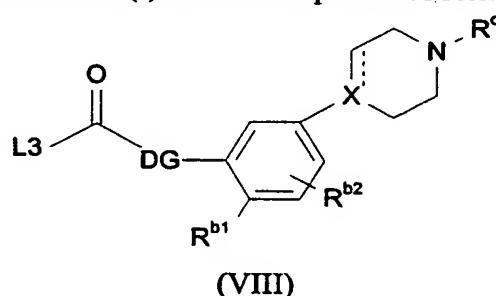


15 in which  $R^a$  is as defined in formula (I), and  $L^3$  is an appropriate leaving group, with a compound of formula (V): or

(e) where L is - Y -C(=O)-DG - in which D is CH and Y is NH, reacting a compound of formula (VI):



in which  $R^a$  is as defined in formula (I) with a compound of formula (VIII):



25 in which G, X,  $R^{b1}$ ,  $R^{b2}$  and  $R^c$  are as defined in formula (I) and  $L^3$  is an appropriate leaving atom; and optionally thereafter:

- removing any protecting groups,
- converting a compound of formula (I) into another compound of formula (I),
- forming a pharmaceutically acceptable salt.

5 In the reaction of the compounds of formulae (II) and (III), suitable examples of groups L<sup>1</sup> and L<sup>2</sup> include:-

L<sup>1</sup> is COL<sup>a</sup> and L<sup>2</sup> is NH<sub>2</sub>.

L<sup>1</sup> is NH<sub>2</sub> and L<sup>2</sup> is COL<sup>a</sup> in which L<sup>a</sup> is an appropriate leaving group.

Suitably one of L<sup>1</sup> and L<sup>2</sup> is an activated carboxylic acid derivative such as an acyl

10 chloride or acid anhydride, and the other is an amine group. Activated compounds of formulae (II) and (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling agent such as dicyclohexylcarbodiimide, carbonyldiimidazole or diphenylphosphorylazide. Preferably L<sup>1</sup> or L<sup>2</sup> is a group COL<sup>a</sup> where L<sup>a</sup> is halo particularly chloro.

15 Compounds of formulae (II) and (III) are typically reacted together in an inert solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as an alkali metal hydroxide, trimethylamine or pyridine.

20 The reaction in process (b) is conveniently effected in an organic solvent such as dichloromethane.

In process (c) the urea forming agent can be carbonyl diimidazole, triphosgene or phosgene, and carried out in an inert organic solvent such as dimethylformamide, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

25 In process (d) the leaving group L<sup>3</sup> may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

30 In process (e) the leaving group L<sup>3</sup> may be a halogen e.g. chloro group and the reaction may be carried out in an inert organic solvent such as tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, in the case wherein R<sup>c</sup> is hydrogen, it is possible to

introduce a C<sub>1</sub>-6alkyl group by conventional alkylation using 1 molar equivalent of a C<sub>1</sub>-6alkyl halide and 1 molar equivalent of a suitable base in an inert solvent.

Intermediate compounds of formula (II) to (VIII) can be prepared using standard procedures known in the art.

5 It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional procedures well known in the art.

10 Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

15 The involvement of serotonin (5-hydroxytryptamine; 5HT) receptors in a number of pharmacological effects has been reviewed by R. A. Glennon in "Serotonin Receptors: Clinical Implications", Neuroscience and Behavioural Reviews, 1990, 14, 35 and by L.O.Wilkinson and C.T. Dourish in "Serotonin Receptor Subtypes : Basic and Clinical Aspects" S. Peroutka Ed., John Wiley and Sons, New York, 1991 p.147.

20 Serotonin receptors have been implicated in pharmacological effects such as mood disorders including depression, seasonal affective disorder and dysthymia, anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnesic disorders and age-associated memory impairment; disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sleep disorders (including disturbances of Circadian rhythm), motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders. Serotonin receptor ligands have been shown to be of use in the treatment of emesis and nausea and may also be of use in endocrine disorders such as hyperlactinaemia, vasospasm (particularly in the cerebral vasculature), cerebellar ataxia and hypertension, as well as disorders of the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction and hypothermia.

25

30

35 Ligands with high affinity for the 5HT<sub>1</sub> receptors are well recognised as having therapeutic utility for the treatment of the above conditions. For example: WO 95/31988 refers to the use of a 5-HT<sub>1D</sub> receptor antagonist in conjunction with a 5-HT<sub>1A</sub> receptor

antagonist to treat CNS (central nervous system), endocrine and GI (gastrointestinal) disorders; K. Rasmussen (Annual Reports in Medicinal Chemistry, (1995) 30, 1) describes the utility of 5-HT<sub>1A</sub> receptor agonists and partial agonists in the treatment of various CNS disorders; P. Trouillas (Progress in Brain Research, C.I. de Zeeuw, P. Stara and J. Voogd, 5 Eds. 1997, 144, 589) and G. Maura (J. Neurochemistry, 1996, 66, 202) propose that administration of agonist ligands selective for the 5-HT<sub>1A</sub> receptor or for both 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> receptors should provide effective treatment for human cerebellar ataxias.

10 The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

15 In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

20 The affinities of the compounds of this invention for the 5HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors can be determined by the following radioligand binding assay. HEK 293 cells expressing 5-HT<sub>1A</sub> receptors ( $4 \times 10^7$ /ml) are homogenised in Tris buffer and stored in 1ml aliquots. CHO cells expressing 5-HT<sub>1B</sub> receptors ( $4 \times 10^7$  cells/ml) are homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing 5-HT<sub>1D</sub> receptors ( $0.563 \times 10^8$ /ml) are homogenised in Tris buffer and stored in 1 ml aliquots.

25 0.4 ml of a cell suspension is incubated with [<sup>3</sup>H]-5-HT (4nM) for 5-HT<sub>1B/1D</sub> receptors and [<sup>3</sup>H]-8-OH DPAT (1nM) for 5-HT<sub>1A</sub> receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37°C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Packard Filtermate (filters pre-soaked in 0.3% polyethylenimine) and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC<sub>50</sub> generated by an iterative least squares curve fitting programme.

30 35 The intrinsic activity of the compounds of this invention can be determined according to the following procedure. HEK293 cell membranes stably expressing human 5-HT<sub>1A</sub> receptors and CHO cell membranes stably expressing human 5-HT<sub>1B</sub> receptors are

homogenised in HEPES/EDTA buffer and stored in 1ml aliquots, and [<sup>35</sup>S]GTP $\gamma$ S binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, 52, 449) with some minor modifications. Membranes from 10<sup>6</sup> cells are pre-incubated at 30°C for 30 min in 20 mM HEPES buffer (pH 7.4) in the presence of MgCl<sub>2</sub> (3 mM), NaCl (100 mM),  
5 GDP (10  $\mu$ M) and ascorbate (0.2 mM), with or without compounds. The reaction is started by the addition of 10  $\mu$ l of [<sup>35</sup>S]GTP $\gamma$ S (100 pM, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding was determined using non-radiolabelled GTP $\gamma$ S (20  $\mu$ M) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice  
10 cold HEPES (20 mM) /MgCl<sub>2</sub> (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [<sup>35</sup>S]GTP $\gamma$ S functional assay.

The compounds of formula (I) show high affinity for the 5HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. It has been found, using the [<sup>35</sup>S]GTP $\gamma$ S functional assay, that certain  
15 compounds of formula (I) show varying levels of intrinsic efficacy, which is defined by a scale ranging from 1.0 to 0 (1 defines the maximum response elicited by the agonist 5-HT, 0 defines antagonism). The difficulties in describing intrinsic activity of drugs acting at G protein coupled receptors is recognised in the art (Hoyer and Boddeke, Trends in Pharmacological Sciences, July 1993, [Vol. 14], page 270-275). We believe that however  
20 these ligands are classified according to this functional assay, the compounds of this invention will be useful antidepressants *in vivo*. It is believed that the preferred compounds of this invention will display 5HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> antagonist activity *in vivo* and that such compounds will have a rapid onset of action. A rapid onset of action is particularly advantageous for antidepressant compounds: by 'rapid onset of action' we mean that a  
25 therapeutic response is seen within 7 days from first administration of the compound, as opposed to a period of about 21 days or more which is typical of SSRI's, tricyclic antidepressants and buspirone.

Compounds of formula (I) which have an intrinsic activity of 0.5 or less in the [<sup>35</sup>S]GTP $\gamma$ S functional assay are particularly preferred, as these compounds are more likely  
30 to be full antagonists *in vivo*. As disclosed in WO 95/31988, the simultaneous antagonism of pre-synaptic 5HT<sub>1A</sub>/1B/1D receptors will result in increased release of 5HT *in vivo* and this will improve 5HT neurotransmission.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, a selective serotonin reuptake inhibitor (SSRI) antidepressant.

5 The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, 10 oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, 15 disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may 20 contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. 25 The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling 30 into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate 35 uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and 5 other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

10

### Description 1

#### 1-Acetyl-6-nitroindoline (D1)

A stirred solution of 6-nitroindoline (100g, 0.61 mol) in dichloromethane (1000 ml) at room temperature was treated dropwise over 20 minutes with acetic anhydride (62 ml, 0.66 mol).

15

The reaction mixture was stirred for a further 2 hours, then washed with 10%  $\text{Na}_2\text{CO}_3$  solution (300 ml), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to afford the title compound as a yellow solid (125g, 100%).

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.95 (d, 1H), 7.87 (dd, 1H), 7.26 (d, 1H), 4.18 (t, 2H), 3.29 (t, 2H), 2.26 (s, 3H).

20

### Description 2

#### 1-Acetyl-6-aminoindoline (D2)

A stirred suspension of 1-acetyl-6-nitroindoline (D1, 125g, 0.61 mol) in THF (5500 ml) was hydrogenated over 10% Pd-C (20g) at 50 psi (344.8KPa) for 20 hours. The catalyst was 25 removed by filtration through a plug of kieselguhr and the filtrate concentrated *in vacuo* to afford the title compound as a beige solid (102g, 95%).

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.64 (d, 1H), 6.92 (d, 1H), 6.34 (dd, 1H), 4.01 (t, 2H), 3.82 (br s, 2H), 3.06 (t, 2H), 2.19 (s, 3H).

30

### Description 3

#### 1-Acetyl-6-(4-methylpiperazin-1-yl)indoline (D3)

A stirred mixture of 1-acetyl-6-aminoindoline (D2, 37.8g, 0.22 mol), mechlorethamine hydrochloride (46g, 0.24 mol) and anhydrous potassium carbonate (80g, 0.58 mol) in 1-butanol (1800 ml) was heated at reflux for 8 hours, then additional mechlorethamine 35 hydrochloride (25g, 0.13 mol) and potassium carbonate (41g, 0.30 mol) were added and

reflux continued for 3 hours. The reaction mixture was allowed to cool and then washed with water (1000 ml). The aqueous wash was extracted with ethyl acetate, and the extract combined with the 1-butanol solution and concentrated *in vacuo*. The brown oily residue (60g) was chromatographed on silica gel eluting with 0-8% MeOH/DCM to give an orange oil, which was triturated with ether to afford the title compound as a beige solid (12.2g, 22%).

5  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.98 (d, 1H), 7.04 (d, 1H), 6.59 (dd, 1H), 4.04 (t, 2H), 3.23-3.18 (m, 4H), 3.10 (t, 2H), 2.60-2.53 (m, 4H), 2.34 (s, 3H), 2.21 (s, 3H).

10 **Description 4**

**1-Acetyl-5-chloro-6-(4-methylpiperazin-1-yl)indoline (D4)**

A stirred solution of 1-acetyl-6-(4-methylpiperazin-1-yl)indoline (D3, 1.1g, 0.0040 mol) in dichloromethane (100 ml) at -5°C under argon was treated dropwise over 15 minutes with a solution of N-chlorosuccinimide (0.73g, 0.0054 mol) in DCM (10 ml), then kept at -5°C for a further 0.5h and allowed to warm to room temperature over 1 hour. The reaction mixture was extracted with 2M HCl acid (60 ml) and the acid extract basified by addition of solid  $\text{K}_2\text{CO}_3$  and extracted with DCM. The organic extract was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to afford the title compound as a beige solid (1.45g, 100%).

15  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.05 (s, 1H), 7.15 (s, 1H), 4.06 (t, 2H), 3.20-3.05 (m, 4H), 3.12 (t, 2H), 2.70-2.55 (m, 4H), 2.37 (s, 3H), 2.22 (s, 3H).

**Description 5**

**5-Chloro-6-(4-methylpiperazin-1-yl)indoline (D5)**

A stirred solution of 1-acetyl-5-chloro-6-(4-methylpiperazin-1-yl)indoline (D4, 1.4g, 0.0048 mol) in 2M HCl acid (120 ml) was heated at reflux under argon for 5 hours. The reaction mixture was allowed to cool, basified by addition of solid  $\text{K}_2\text{CO}_3$  and extracted with DCM. The extract was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo* to afford the title compound as a beige solid (0.93g, 78%).

20  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.07 (s, 1H), 6.40 (s, 1H), 3.76 (br s, 1H), 3.56 (t, 2H), 3.01 (br s, 4H), 2.96 (t, 2H), 2.60 (br s, 4H), 2.35 (s, 3H).

**Description 6**

**1-Acetyl-5-bromo-6-(4-methylpiperazin-1-yl)indoline (D6)**

A stirred mixture of 1-acetyl-6-(4-methylpiperazin-1-yl)indoline (D3, 2.0g, 0.0077 mol) and anhydrous potassium carbonate (2.12g, 0.015 mol) in a mixture of dichloromethane (100 ml)

and methanol (50 ml) at -5°C under argon was treated portionwise over 20 minutes with benzyltrimethylammonium tribromide (3.14g, 0.0081 mol). The mixture was allowed to warm to room temperature over 1 hour, then concentrated *in vacuo* and the residue dissolved in dichloromethane (150 ml), washed with water (2x100 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to afford the title compound as a beige solid (2.52g, 97%).

5 <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 8.06 (s, 1H), 7.34 (s, 1H), 4.06 (t, 2H), 3.13 (t, 2H), 3.07 (br s, 4H), 2.60 (br s, 4H), 2.35 (s, 3H), 2.21 (s, 3H).

### Description 7

#### 10 5-Bromo-6-(4-methylpiperazin-1-yl)indoline (D7)

A solution of 1-acetyl-5-bromo-6-(4-methylpiperazin-1-yl)indoline (D6, 0.60g, 1.8 mmol) in 2M hydrobromic acid (50 ml) was stirred at room temperature for 5 days, then basified by addition of solid K<sub>2</sub>CO<sub>3</sub> and extracted with DCM. The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to afford the title compound as a brown solid (0.31g, 58%).

15 <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) δ (ppm): 7.24 (s, 1H), 6.42 (s, 1H), 3.80 (br s, 1H), 3.56 (t, 2H), 3.01-2.92 (m, 6H), 2.59 (br s, 4H), 2.35 (s, 3H).

### Description 8

#### 5-Nitro-1-tetralone (D8)

20 To a stirred solution of 1-tetralone (14ml, 0.105mol) and trifluoroacetic anhydride (31.0ml, 0.220mol) in CH<sub>2</sub>Cl<sub>2</sub> (70ml) was added ammonium nitrate (8.5g, 0.106mol). After 10 minutes the temperature started to increase, so the flask was immersed in an ice bath for 30 minutes after which the mixture was allowed to warm to room temperature and stirred overnight. The mixture was concentrated and the residue treated with saturated aqueous

25 NaHCO<sub>3</sub> solution until neutral and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x). The organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to a brown semi-solid. The residue was purified using flash chromatography eluting with 0-20% Et<sub>2</sub>O/60-80 petrol to give the title compound as a yellow crystalline solid (2.1g, 10%).

30 <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 8.35 (dd, 1H), 8.09 (dd, 1H), 7.49 (t, 1H), 3.22 (t, 2H), 2.73 (t, 2H), 2.15 (m, 2H).

### Description 9

#### 5-Amino-1-tetralone (D9)

To a stirred mixture of 5-nitro-1-tetralone (D8, 2.1g, 11.0mmol) and SnCl<sub>2</sub> in methanol (50ml) was added conc. HCl (3ml) and the mixture heated at reflux for 3 hours before

allowing to cool overnight. The mixture was concentrated *in vacuo* and the residue partitioned between CH<sub>2</sub>Cl<sub>2</sub> (80ml) and water (10ml). The mixture was made strongly alkaline by addition of 40% NaOH solution, then filtered to remove the insoluble tin residues. The organics were separated and the aqueous extracted further with CH<sub>2</sub>Cl<sub>2</sub> (1x).

5 The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to give the title compound as a dark green solid (1.5g, 85%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ (ppm): 7.53 (dd, 1H), 7.14 (t, 1H), 6.88 (dd, 1H), 3.71 (br s, 2H), 2.60-2.71 (m, 4H), 2.13-2.22 (m, 2H).

10

**Example 1**

**5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline (E1)**

To a stirred solution of triphosgene (40mg, 0.13mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5ml) was added a solution of 5-amino-1-indanone (59mg, 0.4mmol) in triethylamine (0.06ml, 0.4mmol) and 15 CH<sub>2</sub>Cl<sub>2</sub> (5ml) and the mixture stirred under argon for 0.5 hours. To the mixture was added 5-chloro-6-(4-methylpiperazin-1-yl)indoline (D5, 100mg, 0.4mmol) in CH<sub>2</sub>Cl<sub>2</sub> and stirring continued for 16 hours. The mixture was washed with aqueous 10% Na<sub>2</sub>CO<sub>3</sub>, the organics dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo* to a yellow solid. Purification using flash chromatography eluting with 5% MeOH/ CH<sub>2</sub>Cl<sub>2</sub> gave the title compound as a white solid 20 (130mg, 76%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ(ppm): 7.90 (s, 1H), 7.80 (s, 1H), 7.69 (d, 1H), 7.32 (m, 2H), 7.17 (s, 1H), 4.15 (t, 2H), 3.19 (t, 2H), 3.12-3.14 (br s, 4H and t, 2H), 2.65-2.72 (br s, 4H and t, 2H), 2.36 (s, 3H).

25 **Example 2**

**5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline (E2)**

The title compound was prepared from 6-amino-1-tetralone and 5-chloro-6-(4-methylpiperazin-1-yl)indoline (D5) using a similar method to Example 1 (63%).

30 <sup>1</sup>H NMR (250MHz, d<sup>6</sup>DMSO) δ(ppm): 8.92 (s, 1H), 7.86 (m, 2H), 7.69 (d, 1H), 7.62 (dd, 1H), 7.29 (s, 1H), 4.16 (t, 2H), 3.08 (t, 2H), 2.88 (m, 6H), 2.51 (t, 2H), 2.46 (br s, 4H), 2.18 (s, 3H), 1.97 (m, 2H).

**Example 3**

35 **5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline (E3)**

The title compound was prepared from 5-amino-1-indanone and 5-bromo-6-(4-methylpiperazin-1-yl)indoline (D7) using a similar method to Example 1.

$^1\text{H}$  NMR (250MHz, d<sup>6</sup>DMSO)  $\delta$ (ppm): 8.95 (s, 1H), 7.92 (s, 1H), 7.82 (s, 1H), 7.61 (m, 2H), 7.43 (s, 1H), 4.22 (t, 2H), 3.16 (t, 2H), 3.10 (t, 2H), 2.93 (br s, 4H), 2.62 (t, 2H), 2.26 (s, 3H).

5 4 protons (piperazine) obscured by solvent signal.

#### Example 4

**5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline (E4)**

10 The title compound was prepared from 6-amino-1-tetralone and 5-bromo-6-(4-methylpiperazin-1-yl)indoline (D7) using a similar method to Example 1.

$^1\text{H}$  NMR (250MHz, d<sup>6</sup>DMSO)  $\delta$ (ppm): 8.86 (s, 1H), 7.84 (d, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.58 (dd, 1H), 7.43 (s, 1H), 4.17 (m, 4H), 3.15 (t, 2H), 2.94 (br s, 8H), 2.58 (t, 2H), 2.26 (s, 3H), 2.05 (m, 2H).

15

#### Example 5

**5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline (E5)**

The title compound was prepared from 6-amino-1-indanone (EP 0275131) and 5-bromo-6-(4-methylpiperazin-1-yl)indoline (D7) using a similar method to Example 1. This was

20 isolated as the hydrochloride salt.

$^1\text{H}$  NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO)  $\delta$ (ppm): 10.85 (br s, 1H), 8.88 (s, 1H), 7.92 (m, 2H), 7.85 (s, 1H), 7.54 (d, 1H), 7.32 (s, 1H), 4.22 (t, 2H), 3.17 (t, 2H), 3.09 (t, 2H), 2.86 (s, 3H), 2.68 (t, 2H). 8 protons (piperazine) obscured.

25 **Example 6**

**5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline (E6)**

The title compound was prepared from 6-amino-1-indanone (EP 0275131) and 5-chloro-6-(4-methylpiperazin-1-yl)indoline (D5) using a similar method to Example 1. This was isolated as the hydrochloride salt.

30  $^1\text{H}$  NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO)  $\delta$ (ppm): 10.81 (br s, 1H), 8.87 (s, 1H), 7.89 (m, 2H), 7.85 (s, 1H), 7.53 (d, 1H), 7.46 (s, 1H), 4.20 (t, 2H), 3.17 (t, 2H), 3.08 (t, 2H), 2.86 (s, 3H), 2.67 (t, 2H). 8 protons (piperazine) obscured.

#### Example 7

**5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline (E7)**

The title compound was prepared from 7-amino-1-tetralone (EP 0275131) and 5-bromo-6-(4-methylpiperazin-1-yl)indoline (D7) using a similar method to Example 1. This was isolated

5 as its hydrochloride salt.

<sup>1</sup>H NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO) δ(ppm): 11.01 (br s, 1H), 8.82 (s, 1H), 8.11 (d, 1H), 7.86 (m, 2H), 7.45 (s, 1H), 7.30 (d, 1H), 4.20 (t, 2H), 3.16-3.50 (m, 8H), 3.16 (t, 2H), 2.92 (t, 2H), 2.85 (s, 3H), 2.62 (t, 2H), 2.05 (m, 2H).

10 **Example 8**

**5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline (E8)**

The title compound was prepared from 7-amino-1-tetralone (EP 0275131) and 5-chloro-6-(4-methylpiperazin-1-yl)indoline (D5) using a similar method to Example 1. This was isolated

15 as its hydrochloride salt.

<sup>1</sup>H NMR (HCl salt) (250MHz, d<sup>6</sup>DMSO) δ(ppm): 11.00 (br s, 1H), 8.82 (s, 1H), 8.11 (d, 1H), 7.85 (m, 2H), 7.31 (m, 2H), 4.20 (t, 2H), 3.05-3.49(m, 8H), 3.16 (t, 2H), 2.92 (t, 2H), 2.84 (s, 3H), 2.62 (t, 2H), 2.06 (m, 2H).

20 **Example 9**

**5-Chloro-1-(9-oxo-9H-fluoren-2-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline (E9)**

The title compound was prepared from 2-amino-9H-fluoren-9-one and 5-chloro-6-(4-methylpiperazin-1-yl)indoline (D5) using a similar procedure to Example 1, as an orange solid (46%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ(ppm): 7.82 (s, 1H), 7.80 (dd, 1H), 7.61 (d, 1H), 7.55 (d, 1H), 7.49 - 7.46 (m, 3H), 7.26 - 7.23 (m, 1H), 7.15 (s, 1H), 6.58 (s, 1H), 4.12 (t, 2H), 3.20 (t, 2H), 3.11 (br s, 4H), 2.61 (br s, 4H), 2.36 (s, 3H).

30 **Example 10**

**5-Chloro-1-(9-oxo-9H-fluoren-3-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline (E10)**

The title compound was prepared from 3-amino-9H-fluoren-9-one and 5-chloro-6-(4-methylpiperazin-1-yl)indoline (D5) using a similar procedure to Example 1, as a yellow/orange solid (66%).

<sup>1</sup>H NMR (250MHz, d<sup>6</sup> DMSO) δ(ppm): 8.98 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.67 (d, 1H), 7.59 - 7.54 (m, 4H), 7.35 (t, 1H), 7.21 (s, 1H), 4.17 (t, 2H), 3.10 (t, 2H), 2.90 (br s, 4H), 2.48 (br s, 4H), 2.21 (s, 3H).

5 **Example 11**

**5-Methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline (E11)**

The title compound was prepared from 6-amino-1-tetralone and 5-methoxy-6-(4-methylpiperazin-1-yl)indoline (Intermediate 3 in WO 95/06627) using a similar method to

10 Example 1, as a buff solid (96%).

<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>/CD<sub>3</sub>OD) δ (ppm): 7.96 (d, 1H), 7.67 (s, 1H), 7.61 (m, 1H), 7.19 (dd, 1H), 6.74 (s, 1H), 4.09 (t, 2H), 3.84 (s, 3H), 3.12-3.21 (t, 2H and br s, 4H), 2.95 (t, 2H), 2.59-2.64 (t, 2H and br s, 4H), 2.34 (s, 3H), 2.11 (m, 2H). NH not observed.

MS: m/z = 435 (MH<sup>+</sup>)

15

**Example 12**

**5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline (E12)**

The title compound was prepared from 5-amino-1-tetralone (D9) and 5-chloro-6-(4-

20 methylpiperazin-1-yl)indoline (D5) using a similar method to Example 1, as the hydrochloride salt, a buff solid (30%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 10.82 (br s, 1H), 8.54 (s, 1H), 7.46-7.81 (m, 2H), 7.54 (d, 1H), 7.28-7.39 (m, 2H), 4.19 (t, 2H), 3.28-3.57 (m, 4H), 2.99-3.16 (m, 6H), 2.80-2.87 (m, 2H), 2.61 (br m, 2H), 2.08 (d, 3H), 2.00 (br m, 2H).

25 MS: m/z = 439/41 (MH<sup>+</sup>)

**Example 13**

**5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline (E13)**

30 The title compound was prepared from 5-amino-1-tetralone (D9) and 5-bromo-6-(4-methylpiperazin-1-yl)indoline (D7) using a similar method to Example 1, as the hydrochloride salt, a buff solid (35%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 10.67 (br s, 1H), 8.54 (s, 1H), 7.75-7.82 (m, 2H), 7.54 (dd, 1H), 7.44 (s, 1H), 7.36 (t, 1H), 4.19 (t, 2H), 3.47-3.51 (m, 2H), 3.27-3.31

(m, 2H), 3.14-3.20 (m, 2H), 2.94-3.03 (m, 2H), 2.82-2.87 (m, 4H), 2.62 (t, 2H), 2.09 (s, 3H), 2.00 (m, 2H).

MS: m/z = 483/85 (MH<sup>+</sup>)

5 **Example 14**

**5-Methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline (E14)**

The title compound was prepared from 5-amino-1-tetralone (D9) and 5-methoxy-6-(4-methylpiperazin-1-yl)indoline (Intermediate 3 in WO 95/06627) using a similar method to

10 Example 1, as the hydrochloride salt, a buff solid (33%).

<sup>1</sup>H NMR (HCl salt) (250 MHz, d<sup>6</sup>DMSO) δ (ppm): 10.84 (br s, 1H), 8.37 (s, 1H), 7.77 (d, 1H), 7.54-7.59 (m, 2H), 7.34 (t, 1H), 6.92 (s, 1H), 4.15 (t, 2H), 3.76 (s, 3H), 3.35-3.46 (m, 4H), 3.15 (m, 2H), 2.78-2.98 (m, 6H), 2.61 (t, 2H), 2.50 (s, 3H), 2.00 (t, 2H).

MS: m/z = 435 (MH<sup>+</sup>)

15

**Pharmacological Data**

The affinities of the compounds of this invention were determined by methods described

20 above.

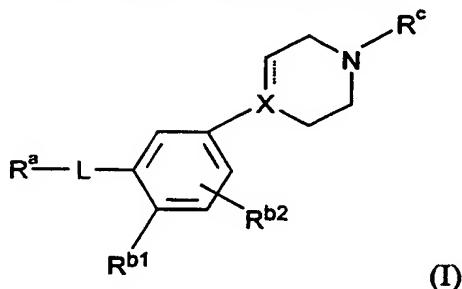
**5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> Receptor Binding**

Examples 1, 2, 3, 4, 9, 10, 11 and 14 had pKi values > 7.5 at 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub>

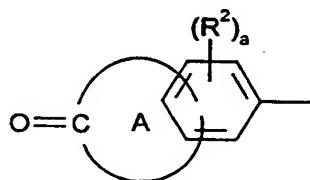
25 receptors.

## CLAIMS

1. A compound of formula (I) or a salt thereof:



5 in which  $R^a$  represents the group:



in which the ring A is 5, 6 or 7 -membered carbocyclic ring optionally substituted by one or  
 10 more  $C_1$ -6alkyl groups, fused at the 2,3- or 3,4-positions of the adjacent phenyl ring, the ring  
 A being optionally fused to a further phenyl ring optionally substituted by one or more  
 substituents independently selected from  $C_1$ -6alkyl and halo;

$R^2$  is halogen,  $C_1$ -6alkyl,  $C_3$ -6cycloalkyl,  $C_3$ -6cycloalkenyl,  $C_1$ -6alkoxy,  $C_1$ -6alkanoyl,  
 aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano,  $CO_2R^{10}$ ,  $CONR^{10}R^{11}$ ,  $NR^{10}R^{11}$   
 15 where  $R^{10}$  and  $R^{11}$  are independently hydrogen or  $C_1$ -6alkyl;

$a$  is 0, 1 or 2;

L is a group of formula

-  $Y-C(=O)-DG$  - or -  $C(=O)-DG$  - or -  $DG-C(=O)$  -

in which Y is -  $NH$  -,  $NR^5$  where  $R^5$  is  $C_1$ -6alkyl, or Y is -  $CH_2$  - or -  $O$  -;

20 D is nitrogen, carbon or a CH group, G is hydrogen or  $C_1$ -6alkyl providing that D is nitrogen  
 or a CH group, or G together with  $R^{b1}$  forms a group W where W is  $(CR^{16}R^{17})_t$  where t is  
 2, 3 or 4 and  $R^{16}$  and  $R^{17}$  are independently hydrogen or  $C_1$ -6alkyl or W is  $(CR^{16}R^{17})_u-J$   
 where u is 0, 1, 2 or 3 and J is oxygen, sulphur,  $CR^{16}=CR^{17}$ ,  $CR^{16}=N$ ,  $=CR^{16}O$ ,  $=CR^{16}S$   
 or  $=CR^{16}-NR^{17}$  provided that u is not 0 when J is oxygen or sulphur;

25 X is nitrogen or carbon;

$R^{b1}$  and  $R^{b2}$  are independently hydrogen, halogen, hydroxy,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{3-6}$ cycloalkyl, trifluoromethyl,  $C_{1-6}$ alkoxy or aryl, or  $R^{b1}$  together with G forms a group W as defined above;

$R^c$  is hydrogen or  $C_{1-6}$ alkyl; and

5  $\underline{\underline{}}$  is a single bond when X is nitrogen or a single or double bond when X is carbon.

2. A compound according to claim 1 in which the ring A is a 5 or 6-membered ring in which the oxo group is attached to a carbon atom adjacent to the phenyl ring.

10 3. A compound according to claim 1 or 2 in which  $R^2$  is halogen or a  $C_{1-6}$  alkyl group.

4. A compound according to any of the preceding claims in which the group L is a group of formula:-  $-Y-C(=O)-(DG)-$

15 in which Y, D and G are as defined above.

5. A compound according to any of the preceding claims in which Y is  $-NH-$ .

6. A compound according to any of the preceding claims in which D is nitrogen  
20 and W is a group of formula  $-(CH_2)_2-$ .

7. A compound according to any of the preceding claims in which  $R^{b1}$  and  $R^{b2}$  are independently hydrogen, halogen or  $C_{1-6}$ alkoxy.

25 8. A compound according to any of the preceding claims in which X is nitrogen.

9. A compound according to claim 1 which is:

5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline,

5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-

30 naphthalenyl)aminocarbonyl]indoline,

5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-5-yl)aminocarbonyl]indoline,

5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline,

5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline,

35 5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(1-oxoindan-6-yl)aminocarbonyl]indoline,

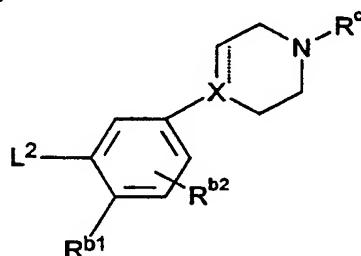
5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline,  
 5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-8-oxo-2-naphthalenyl)aminocarbonyl]indoline,  
 5-Chloro-1-(9-oxo-9H-fluoren-2-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline,  
 5-Chloro-1-(9-oxo-9H-fluoren-3-ylaminocarbonyl)-6-(4-methylpiperazin-1-yl)indoline,  
 5-Methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)aminocarbonyl]indoline,  
 5-Chloro-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline,  
 5-Bromo-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline,  
 5-Methoxy-6-(4-methylpiperazin-1-yl)-1-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)aminocarbonyl]indoline  
 15 or a pharmaceutically acceptable salt thereof.

10. A process for the preparation of a compound of formula (I) which comprises:

(a) where L is  $-C(=O)-DG$  - or  $-DG-C(=O)-$ , coupling a compound of formula (II):

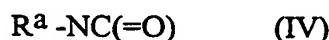


with a compound of formula (III):

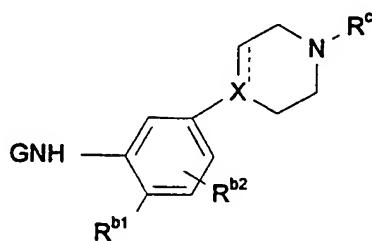


in which  $R^a$ ,  $R^{b1}$ ,  $R^{b2}$ ,  $R^c$  and X are as defined in formula (I) and  $L^1$  and  $L^2$  contain the appropriate functional groups which are capable of reacting together to form the L moiety; or

(b) where L is  $-Y-C(=O)-DG$  in which D is nitrogen and Y is NH, coupling a compound of formula (IV):



in which  $R^a$  is as defined in formula (I) or a protected derivative thereof, with a compound of formula (V):

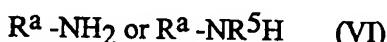


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(V)

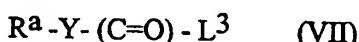
in which  $R^{b1}$ ,  $R^{b2}$ ,  $R^c$ , G and X are as defined in formula (I), or a protected derivative thereof; or

10 (c) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is NH or  $NR^5$ , reacting a compound of formula (VI)



in which  $R^a$  and  $R^5$  are as defined in formula (I) with a compound of formula (V) together with an appropriate urea forming agent; or

15 (d) where L is - Y -C(=O)-DG - in which D is nitrogen and Y is  $CH_2$  or O, reacting a compound of formula (VII):



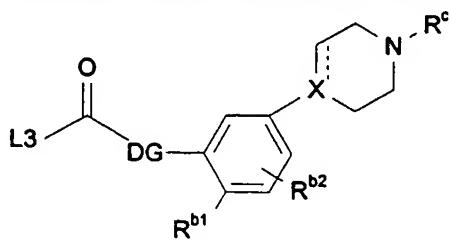
in which  $R^a$  is as defined in formula (I), and  $L^3$  is an appropriate leaving group, with a compound of formula (V); or

20

(e) where L is - Y -C(=O)-DG - in which D is CH and Y is NH, reacting a compound of formula (VI):



in which  $R^a$  is as defined in formula (I) with a compound of formula (VIII):



25

(VIII)

in which G, X, R<sup>b1</sup>, R<sup>b2</sup> and R<sup>c</sup> are as defined in formula (I) and L<sup>3</sup> is an appropriate leaving atom;

and optionally thereafter:

5     • removing any protecting groups,  
• converting a compound of formula (I) into another compound of formula (I),  
• forming a pharmaceutically acceptable salt.

11.   A compound according to any of claims 1 to 9 for use in therapy.

10

12   A compound according to any of claims 1 to 9 for use in the treatment of depression.

13.   A pharmaceutical composition which comprises a compound according to any  
15   of claims 1 to 9 and a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/07803

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 C07D209/08 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 04729 A (SMITHKLINE BEECHAM PLC) 16 February 1995 cited in the application see the whole document ---	1-13
Y	WO 95 06044 A (SMITHKLINE BEECHAM PLC) 2 March 1995 cited in the application see the whole document ---	1-13
Y	WO 95 06637 A (SMITHKLINE BEECHAM PLC) 9 March 1995 cited in the application see the whole document ---	1-13
P, Y	WO 98 47885 A (SMITHKLINE BEECHAM PLC) 29 October 1998 see the whole document ---	1-13
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

27 April 1999

14/05/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Hartrampf, G

**INTERNATIONAL SEARCH REPORT**

Int.	Application No.
PCT/EP	98/07803

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	STARKEY S.J. & SKINGLE M.: "5-HT1D as well as 5-HT1A autoreceptors modulate 5-HT release in the guinea-pig dorsal Raphé nucleus" NEUROPHARMACOLOGY, vol. 33, no. 3/4, 1994, pages 393-402, XP000654898 ---	1-13
A	PAUWELS P.J. & PALMIER C.: "Functional effects of the 5-HT1D receptor antagonist GR 127,935 at human 5-HT1D.alpha., 5-HT1D.beta., 5-HT1A and opossum 5-HT1B receptors" EUROPEAN JOURNAL OF PHARMACOLOGY. MOLECULAR PHARMACOLOGY SECTION, vol. 290, no. 2, 1995, pages 95-103, XP000612639 -----	1-13

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Information on patent family members

International Application No

CT/EP 98/07803

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